Synthesis of novel 1-thia-5,9-diaza-spiro[5.5]undec-2-ene and its recyclization to 1,5,9-triaza-spiro[5.5]undec-2-ene and/or spiro(piperidine-4,2'-thieno[2,3-*d*]pyrimidine)

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Abstract
An efficient and direct procedure for the synthesis of 1-thia-5,9-diaza-spiro[5.5]undec-2-ene has been described. The base-catalyzed recyclization of the latter has been studied. The structures of the products were proved by elemental analyses, IR, MS, ^{1}H- and ^{13}C- NMR spectroscopy.

Keywords: Spiro-piperidine, spiro-1,3-thiazine, spiro-pyrimidine, spiro-thieno[2,3-*d*]pyrimidine

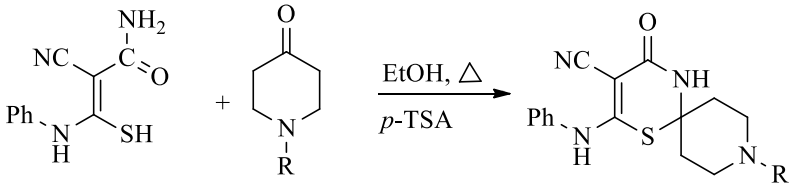
Introduction

Spiro heterocyclic compounds are well known to possess varied pharmacological activities and hence their synthesis has always been a challenge and of attraction to organic chemists. These compounds, display pronounced antimicrobial,[1] analgesic,[2] anti-inflammatory,[2] antimycobacterial,[3] antifungal,[4] antitumor[5,6] and antiviral[5,6] activities. Among these heterocycles, spiropiperidines have been identified as privileged structures in medicinal chemistry[7] and have attracted increasing interest in the past five years. The most recent reports are representative of their wide range of biological activities as components of new SCD-1 inhibitors,[8] nociceptin receptor ligands,[9] CCR5 antagonists,[10] NPYY[11] receptor antagonists,[11] CGRP receptor antagonists,[12] tryptase inhibitors,[13] PGD2 receptor antagonists[14] and ChK1 kinase inhibitors.[15]

Furthermore, 1,3-thiazines are an important type of heterocycles showing a wide variety of pharmacological properties.[16-20] Prompted by the aforesaid biological and pharmaceutical activities, and as a part of our continuing interest on the synthesis of new polyfunctionally substituted heterocyclic[21-30] and spiro heterocyclic compounds[31-34] of expected biological activity, we now report the versatile and hitherto unreported synthesis of 1-thia-5,9-diaza-spiro[5.5]undec-2-ene, and its base-catalyzed recyclization to 1,5,9-triaza-spiro[5.5]undec-2-ene and spiro(piperidine-4,2'-thieno[2,3-*d*]pyrimidine) derivatives with the purpose of investigating in the future their possible biological activity.

Results and Discussion

Scheme 1 outlines the synthesis of the ethyl ester of 3-cyano-4-oxo-2-phenylamino-1-thia-5,9-diaza-spiro[5.5]undec-2-ene-9-carboxylic acid **3a,b** from the cyclocondensation of 2-cyano-3-mercapto-3-phenylamino-acrylamide **1** with ethyl 4-oxo-piperidine-1-carboxylate **2a** and/or 1-benzylpiperidin-4-one **2b** in the presence of catalytic amounts of *p*-toluenesulfonic acid (*p*-TSA) in boiling ethanol.

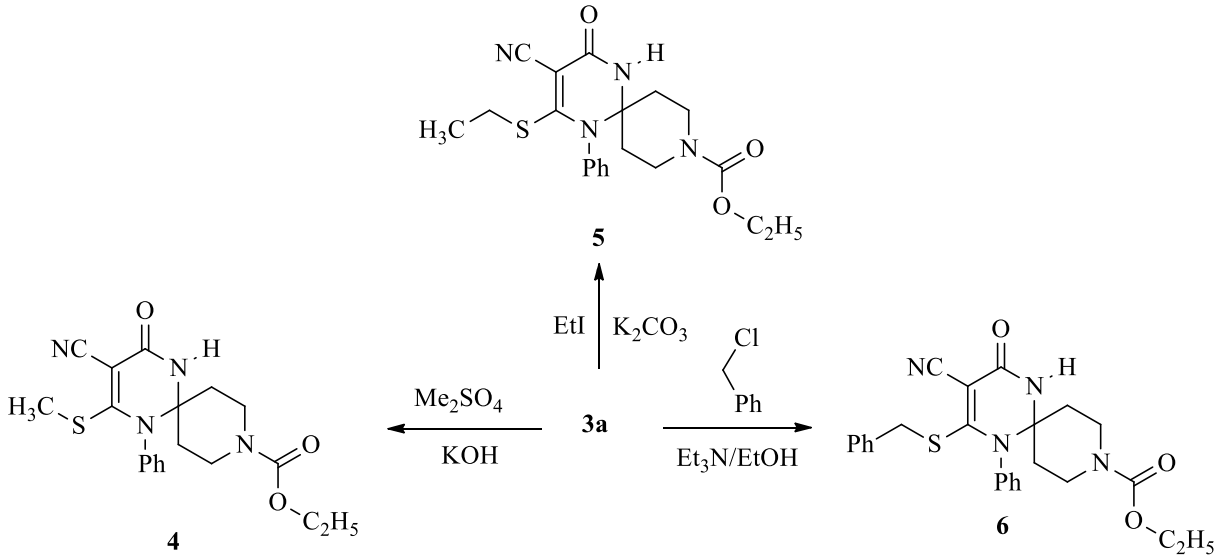


1 **2a,** R = COOEt **b,** R = CH_2Ph **3a,** R = COOEt **b,** R = CH_2Ph

Scheme 1

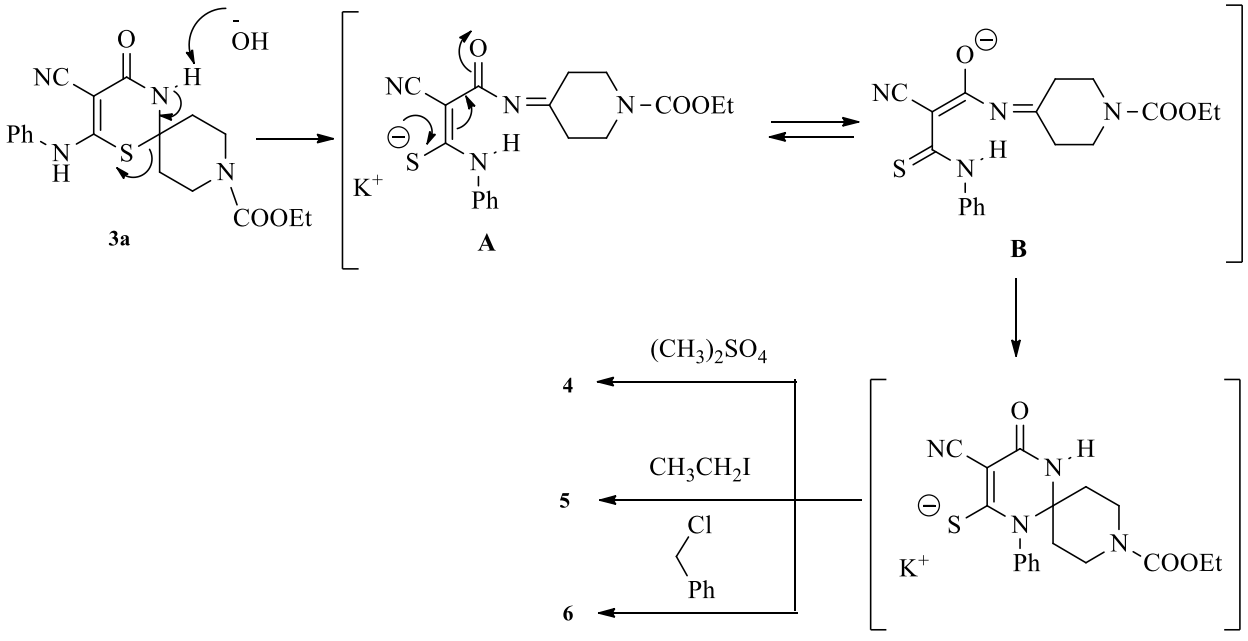
The structure of compounds **3a,b** was determined by elemental analysis, spectroscopic data and the chemical transformations outlined below. Thus, compound **3a** exhibits an IR spectrum with strong absorption bands at 3157, 2205 and 1675 cm^{-1} corresponding to the NH, CN and CO, respectively. Its ^1H NMR spectrum shows characteristic singlets at δ 10.11 and 8.22 ppm for the exocyclic and endocyclic NH protons, respectively, in addition to an eight-proton- multiplet in the region of δ 1.93–3.67 due to the methylene protons, and a multiplet at δ 7.23–7.42 ppm for the aromatic protons. Moreover, the ^{13}C NMR spectrum of **3a** shows signals at δ_C 63.37, 163.86 and 164.48 ppm corresponding to the quaternary sp^3 carbon (spiro carbon) and two carbonyl groups of the ester group and thiazine ring respectively. In addition to signals at δ_C 14.47 (CH_3), 36.27 ($2CH_2$), 38.73 ($2CH_2$), 60.85 (OCH_2), 76.91(C-3), 116.00 (CN), 120.50, 120.72, 125.32, 125.54, 126.75, 128.94, 137.98 (C-Ar) and 154.32 (C=O, ester). The structure assigned for compound **3a** was fully supported by its mass spectrum, which showed a molecular formula $C_{18}H_{20}N_4O_3S$ (*m/z* (%) = 372.00 (M^+, 78.30).

Next, we moved on to study the alkylation of **3a** using dimethyl sulfate, ethyl iodide, and benzyl chloride as alkylating agents under basic conditions (Scheme 2). The reaction proved to involve the sulfur atom, thus affording the S-alkylated derivatives **4-6** (Scheme 2). The structural assignments of compounds **4-6** were confirmed by their spectroscopic data. The distinction between the thiazine and pyrimidine structural types is clearly manifested in the ^1H- and ^{13}C-NMR spectra. For example, the ^1H NMR spectrum of **4** showed the absence of exocyclic NH proton, and in its ^{13}C NMR spectrum the resonance of the aminal carbon atom in compound **4** (δ 73.41) are shifted downfield from those of the thioaminal carbon atom in compound **3a**.



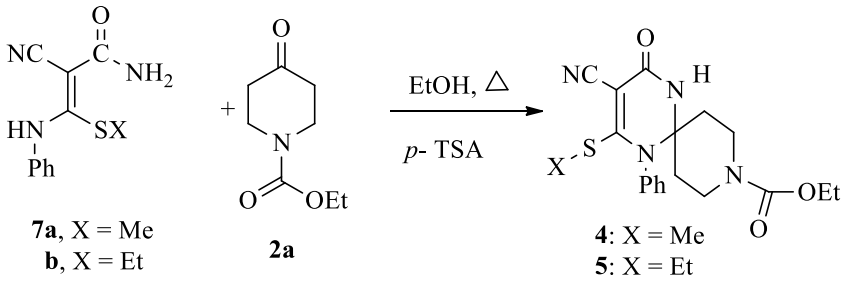
Scheme 2

According to the literature survey, few examples of Dimroth rearrangements are known which involve the transformation of amino-1,3-thiazines to pyrimidinethiones.[21,35,36] From this evidence, the mechanistic picture for the pyrimidine forming process emerged as shown in Scheme 3. Seemingly, a base causes proton abstraction from the nitrogen atom in position 5 and thiazine ring- opening to afford the intermediate **A** which possesses a thio-keto enolic equilibrium forming intermediate **B**, which allows free rotation around the single bond affording the E- diastereomer that could close to the pyrimidines **4**, **5** and **6**, respectively.



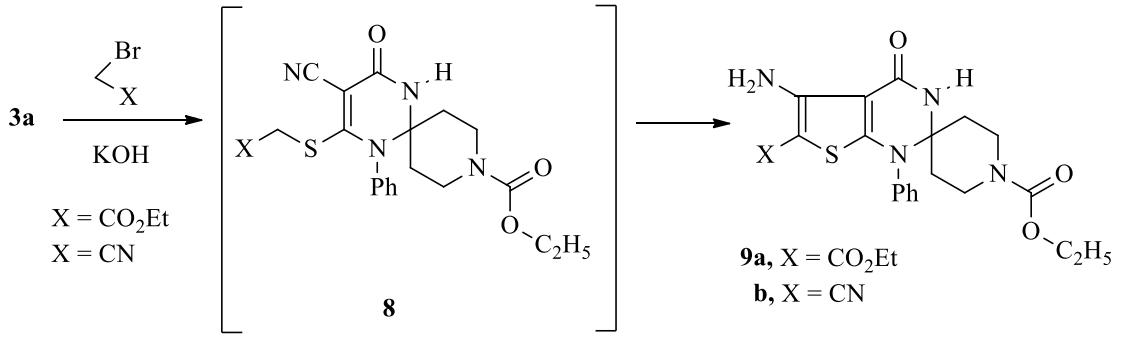
Scheme 3

In addition, formation of the pyrimidines **4** and **5** was further confirmed by an alternative synthesis. Thus, the reaction of **7a**,**b** with 4-oxo-piperidine-1-carboxylic acid ethyl ester **2a** in boiling ethanol, in the presence of catalytic amounts of *p*-toluenesulfonic acid (*p*-TSA) afforded **4** and/or **5** in excellent yields (Scheme 4). The identity of the products prepared in Scheme 4 with those obtained previously in Scheme 2 was confirmed by comparison of their IR and ^{1}H NMR spectra.



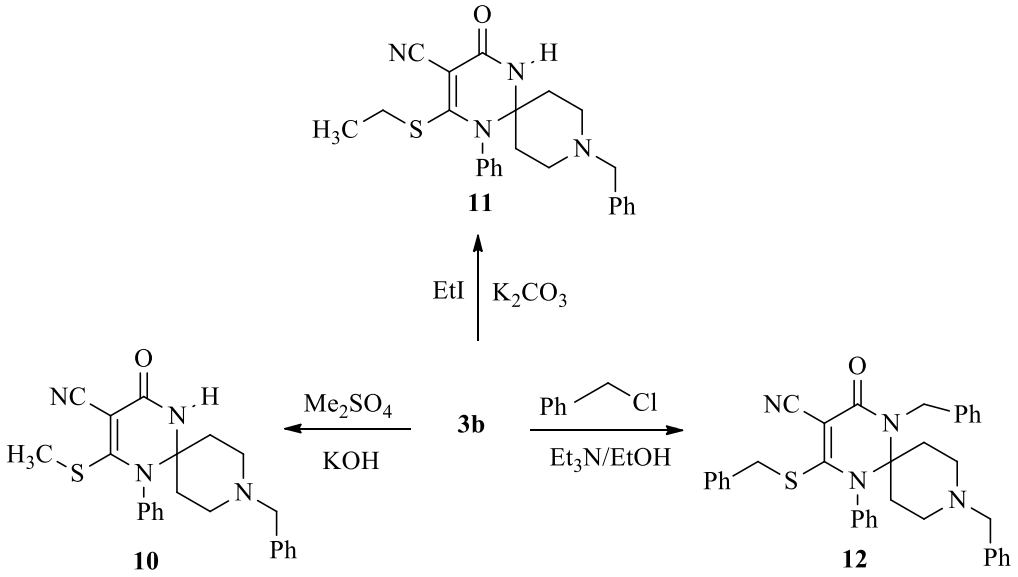
Scheme 4

Treatment of **3a** with ethyl bromoacetate and/or bromoacetonitrile, in aq. KOH furnished the spiro-thienopyrimidine derivatives **9a,b** (Scheme 5). The structures of **9a,b** were established by their correct analyses and compatible spectroscopic data. The IR and ^{1}H- NMR spectra of **9a** revealed the absence of the CN group, signals attributable to the exocyclic NH proton of **3a**, and the presence of signal attributable to the NH_2 protons at δ 6.85 ppm which exchange with D_2O. Furthermore, the fragmentation patterns of the mass spectra of **9a** and **9b** show molecular ion peaks at *m/z* 458.70 (M^+, 48.3%) and *m/z* 411.65 (M^+, 89.36%), respectively, which are in good agreement with the assigned structure. The structures of **9a,b** are rationalized in terms of the initial formation of the intermediate **8**, which on subsequent intramolecular cyclization under the reaction conditions affords the final product .



Scheme 5

Similarly, compound **3b** was reacted with alkylating reagents such as dimethyl sulfate and ethyl iodide under basic conditions to give the corresponding *S*-alkylated derivatives **10** and **11** (Scheme 6).

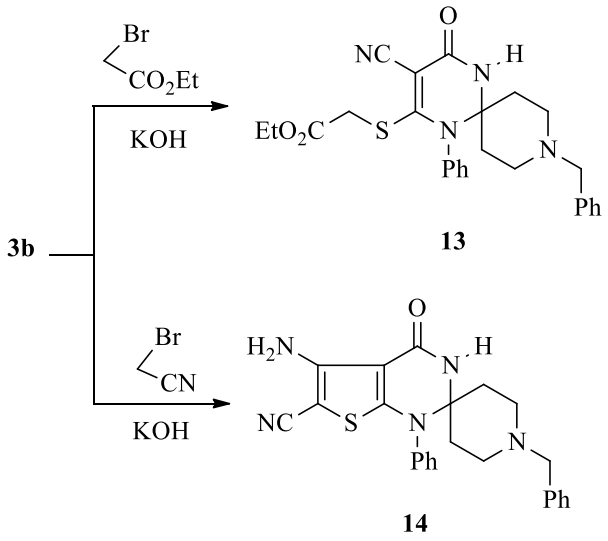


Scheme 6

The molecular formulae of compounds **10** and **11** are supported by elemental analyses and mass spectra that gave the expected molecular ion peaks and their corresponding fragmentation patterns. The IR as well as the ^{1}H NMR spectra agree with the proposed structures. The reaction of the spirothiazine **3b** with benzyl chloride in EtOH in the presence of triethylamine did not afford the expected *S*-benzylated derivative, but rather the dibenzylated derivative **12** (Scheme 6). Both the mass spectrum and elemental analysis established the molecular formula of **12** as $C_{36}H_{34}N_4OS$. The IR and ^{1}H- NMR spectra of **12** revealed the absence of NH group and signals attributable to the endo- and exo-cyclic NH protons of **12**, respectively. Furthermore, the structure assigned for compound **12** was fully supported by their ^{13}C NMR.

The alkylation of **3b** with ethyl bromoacetate in aq. KOH gave the spiro S-substituted thiopyrimidine **13** (Scheme 7), whose elemental analysis and spectral data are in good agreement with the proposed structure. The IR spectrum revealed the presence of CN group with strong absorption band at 2196, NH group at 3145 and CO (ester group) at 1698 cm^{-1}. The ^{1}H NMR of **13** revealed the presence of signals at δ = 3.70 and 8.17 attributable to the SCH_2 and NH protons, respectively. Moreover the mass spectrum of **13** exhibited a molecular ion peak at m/z = 476.20 (M^+, 52.54%). On the other hand, the alkylation of **3b** with bromo-acetonitrile under the previous conditions gave the spiro-thienopyrimidine **13** (Scheme 7). Depending upon the spectroscopic data the structure of compound **14** is undoubtedly confirmed. Thus, the ^{1}H- NMR of **14** revealed the absence of signals attributable to the exocyclic NH proton of **3b**, and the presence of signal

attributable to the NH_2 protons. The mass spectrum of **14** showed the molecular ion peak *m/z* = 429.60 (M^+, 65.59%) corresponding to the molecular formula $C_{14}H_{10}N_4OS$.



Scheme 7

Experimental Section

General. Melting points were measured with a Gallenkamp apparatus and are uncorrected. The reactions and purity were monitored by thin layer chromatography (TLC) on aluminum plates coated with silica gel with fluorescent indicator (Merck, 60 F_{254}) using $CHCl_3$ / CH_3OH (10:1) as eluent. Infrared spectra were recorded on a Jasco FT/IR-450 Plus spectrophotometer. The NMR spectra were obtained on a JHA-LAA 400 WB-FT spectrometer at 400 MHz for ^{1}H- NMR, and 100 MHz for ^{13}C, with $CDCl_3$ and DMSO-d_6 as solvent. Chemical shifts are quoted in δ and are referenced to TMS or the solvent signal. The mass spectra were recorded on a Trace GC 2000 / Finnegan Mat SSQ 7000 and Shimadzu GCMS-QP-1000EX mass spectrometer at 70 eV. Elemental analyses were measured with a Vario EL III CHNOS Elemental Analyzer, Germany, in the Microanalytical Center of Cairo University. Compounds **1**,[37] **7a**,[38] and **7b**,[21] were synthesized using the published procedures.

General procedure for synthesis of 1-thia-5,9-diazaspiro[5.5]undec-2-ene (3a,b)

A mixture of compound **1** (10 mmol), piperidine-4-one **2a,b** (10 mmol) and *p*-toluenesulfonic acid (2 mmol) was refluxed in ethanol (20 mL). A pale yellow precipitate was formed after 4-6 h, the precipitate was filtered off, washed with ethanol, dried and recrystallized from DMF/EtOH.

Ethyl 3-cyano-4-oxo-2-phenylamino-1-thia-5,9-diazaspiro[5.5]undec-2-ene-9-carboxylate (3a). Pale yellow crystals, yield (78%, mp 220°C, IR (υ_{max}, cm^{-1}): 3157 (2-NH), 3028 (Ar-H), 2931 (Alph-H), 2205 (CN), 1675 (C=O, ester), 1632 (C=O). ^{1}H NMR (300 MHz, DMSO-d_6), δ_H 1.16 (3H, t, J = 7.0 Hz, CH_3), 1.93-2.08 (4H, m, $2CH_2$), 3.15-3.22(2H, m, CH_2), 3.60-3.67 (2H, m, CH_2), 4.04 (2H, q, J = 7.2 Hz, OCH_2), 7.23-7.42 ($5H_{arom}$, m, 5CH), 8.22 (1H, s, NH, D_2O-exchangeable), 10.11 (1H, s, NH, D_2O-exchangeable). ^{13}C NMR (75 MHz, DMSO-d_6), δ_C 14.47 (CH_3), 36.27 ($2xCH_2$), 38.73 ($2CH_2$), 60.85 (OCH_2), 63.37 (C-6), 76.91(C-3), 116.00 (CN), 120.50, 120.72, 125.32, 125.54, 126.75, 128.94, 137.98, 146.56 (C-Ar), 154.32 (C=O, ester), 163.86 (C=O), 164.48 (C-2). MS, *m/z*, (%) = 372.00 (M^+, 78.30), 171.05 ($C_{10}H_6N_2OH$, 100). Anal. Calcd for $C_{18}H_{20}N_4O_3S$ (372.44): C, 58.05; H, 5.41; N, 15.04; S, 8.61%, Found: C, 57.97; H, 5.52; N, 14.99; S, 8.56%.

9-Benzyl-4-oxo-2-phenylamino-1-thia-5,9-diazaspiro[5.5]undec-2-ene-3-carbonitrile (3b). Pale yellow crystal, yield 76%, mp 212-214 °C, IR (υ_{max}, cm^{-1}): 3252 (2NH), 3059 (Ar-H), 2942 (Alph-H), 2198 (CN), 1640 (C=O). ^{1}H NMR (300 MHz, DMSO-d_6), δ_H 1.98-2.07 (4H, m, $2CH_2$), 2.11-2.24 (2H, m, CH_2), 2.62-2.66 (2H, m, CH_2), 3.49 (2H, s, NCH_2Ph), 7.21-7.42 ($10H_{aro}$, m, 10CH), 8.19 (1H, s, NH), 10.20 (1H, s, NH). ^{13}C NMR (75 MHz, DMSO-d_6), δ_C 36.62 ($2CH_2$), 48.69 ($2CH_2$), 61.29 (NCH_2Ph), 63.46 (C-6), 76.95(C-3), 116.14 (CN), 125.37, 126.64, 127.05, 128.14, 128.83, 128.91, 131.33, 137.48, 138.06 (C-Ar), 163.80 (C=O), 164.15 (C-2). Anal. Calcd for $C_{22}H_{22}N_4OS$ (390.50): C, 67.67; H, 5.68; N, 14.35; S, 8.21%, Found: C, 67.61; H, 5.76; N, 14.29; S, 8.14%.

Ethyl 3-cyano-2-methylthio-4-oxo-1-phenyl-1,5,9-triazaspiro[5.5]undec-2-ene-9-carboxylate (4). To a stirred 0.75 N aqueous KOH solution (20 mL), compound **3a** (10 mmol) and dimethyl sulfate (20 mmol) were added successively. A resulting precipitate was filtered off, washed with water, dried and recrystallized from ethanol. White powder, yield 84%, mp 220-224 °C, IR (υ_{max}, cm^{-1}): 3216 (NH), 3059 (Ar-H), 2958 (Alph-H), 2212 (CN), 1690 (C=O, ester), 1646 (C=O). ^{1}H NMR (300 MHz, DMSO-d_6), δ_H 1.12 (3H, t, J = 6.6 Hz, CH_3), 1.54-1.62 (2H, m, CH_2), 1.90-194 (2H, m, CH_2), 2.33 (3H, s, SCH_3), 3.70-3.95 (4H, m, $2CH_2$), 3.99 (2H, q, J = 6.9 Hz, OCH_2), 7.33-7.44($5H_{arom}$, m, 5CH), 8.41 (1H, s, NH). ^{13}C NMR (75 MHz, [DMSO-d_6), δ_C 14.46 (CH_3), 17.06 (SCH_3), 33.69 ($2CH_2$), 38.66 ($2CH_2$), 60.78 (OCH_2), 73.41 (C-6), 85.45 (C-3), 116.47 (CN), 129.13, 129.27, 129.88, 138.59 (C-Ar), 154.17 (C=O), 161.02 (C=O), 166.14 (C-2). Anal. Calcd for $C_{19}H_{22}N_4O_3S$ (386.47): C, 59.05; H, 5.74; N, 14.50; S, 8.30%, Found: C, 58.97; H, 5.82; N, 14.41; S, 8.23%.

Ethyl 3-cyano-2-ethylthio-4-oxo-1-phenyl-1,5,9-triazaspiro[5.5]undec-2-ene-9-carboxylate (5). Ethyl iodide (2 mmol) was added to a mixture of **3a** (10 mmol) and anhydrous potassium carbonate (20 mmol) in DMF (5mL). The reaction mixture was stirred for 18-20 h at room temperature and then poured into cold water. After stirring for 15 minutes, the precipitated product was collected by filtration, washed with water, dried and recrystallized from ethanol. Yellow crystal, yield 76%, mp 230 °C, IR (υ_{max}, cm^{-1}): 3216 (NH), 3057 (Ar-H), 2963 (Alph-H), 2212 (CN), 1685 (C=O, ester), 1646 (C=O). ^{1}H NMR (300 MHz, DMSO-d_6), δ_H 1.08-1.15 (6H, m, $2CH_3$), 1.59-1.64 (2H, m, CH_2), 1.91-1.95 (2H, m, CH_2), 2.82 (2H, q, J = 7.2 Hz, SCH_2), 3.04

(2H, m, CH_2), 3.82-3.86 (2H, m, CH_2), 3.98 (2H, q, J = 7.2 Hz, OCH_2), 7.31-7.46 ($5H_{aro}$, m, 5CH), 8.43 (1H, s, NH). ^{13}C NMR (75 MHz, DMSO-d_6), δ_C 14.40 (CH_3), 14.46 (CH_3), 28.24 (SCH_2), 33.71 ($2CH_2$), 38.95 ($2CH_2$), 60.77 (OCH_2), 73.48 (C-6), 87.11(C-3), 116.87 (CN), 129.11, 129.23, 129.87, 138.74 (C-Ar), 154.16 (C=O, ester), 160.87 (C=O), 163.99 (C-2). MS, *m/z*, (%) = 400.30 (M^+, 11.16), 169.00 ($C_8H_{13}N_2O_2$, 100). Anal. Calcd for $C_{20}H_{24}N_4O_3S$ (400.49): C, 59.98; H, 6.04; N, 13.99; S, 8.01%, Found: C, 59.93; H, 6.16; N, 13.89; S, 7.95%.

Ethyl 3-cyano-2-benzylthio-4-oxo-1-phenyl-1,5,9-triazaspiro[5.5]undec-2-ene-9-carboxylate (6). A mixture of compound **3a** (10 mmol), benzyl chloride (10 mmol), and triethylamine (2.1 mL, 1.5 mmol) in ethanol (20 mL), the reaction was continued for 2h., a white precipitate was formed after cooling. A resulting precipitate was filtered off, dried, and recrystallized from ethanol. White crystal, yield 80%, m. p. 240 °C, IR (υ_{max}, cm^{-1}): 3278 (NH), 3043 (Ar-H), 2981 (Alph-H), 2214 (CN), 1689 (C=O, ester), 1647 (C=O). ^1H NMR (300 MHz, DMSO-d_6), δ_H 1.10 (3H, t, J = 7.2 Hz, CH_3), 1.44-1.52 (2H, m, CH_2), 1.80-1.84 (2H, m, CH_2), 2.96-3.04 (2H, m, CH_2), 3.77-3.82 (2H, m, CH_2), 3.99 (2H, q, J = 7.2 Hz, OCH_2), 4.14 (2H, s, J = 7.2 Hz, SCH_2), 7.07-7.45 ($10H_{aro}$, m, 10CH), 8.36 (1H, s, NH). MS, *m/z*, (%) = 462.15 (M^+, 10.45), 91.05 (C_7H_7, 100). Anal. Calcd for $C_{25}H_{26}N_4O_3S$ (462.56): C, 64.91; H, 5.67; N, 12.11; S, 6.93%, Found: C, 64.82; H, 5.77; N, 12.03; S, 6.89%.

Alternative synthesis of (4) and (5). A mixture of 4-oxo-piperidine-1-carboxylic acid ethyl ester **2a** (0.01 mol), **7a**, **b** (0.01 mol), and *p*-toluenesulfonic acid (0.01 mol) in ethanol (20 mL) was refluxed. A precipitate was formed after 7 h. The precipitate was filtered off, washed with ethanol, dried and recrystallized from ethanol.

General procedure for synthesis of spiro(piperidine-4,2'-thieno[2,3-d]pyrimidine) (9a,b)

To a stirred 0.75 N aqueous KOH solution (20 mL), compound **3a** (10 mmol) and ethyl bromoacetate or bromoacetonitrile (20 mmol) were added successively. A resulting precipitate was filtered off, washed with water, dried and recrystallized from ethanol.

Ethyl 5'-amino-4'-oxo-1'-phenyl-3',4'-dihydro-1'H-spiro[piperidine-4,2'-thieno[2,3-d]-pyrimidine]-1,6'-dicarboxylate (9a). White crystal, yield 74%, mp 230-232 °C, IR (υ_{max}, cm^{-1}): 3478-3359 (NH_2), 3202 (NH), 2972 (Alph-H), 1704 (C=O, ester), 1671 (C=O, ester), 1632 (C=O). ^1H NMR (300 MHz, DMSO-d_6), δ_H 1.07-1.15 (6H, m, $2CH_3$), 1.47-1.48 (2H, m, CH_2), 2.12-2.16 (2H, m, CH_2), 3.13-3.25 (2H, m, CH_2), 3.81-3.86 (2H, m, CH_2), 3.95 (2H, q, J = 7.2 Hz, OCH_2), 4.03 (2H, q, J = 7.2 Hz, OCH_2), 6.85 (2H, s, NH_2, D_2O-exchangeable), 7.41-7.56 ($5H_{aro}$, m, 5CH), 8.28 (1H, s, NH, D_2O-exchangeable). MS, *m/z*, (%) = 458.70 (M^+, 48.30%), 242.20 ($C_{12}H_8N_3OS$, 100%). Anal. Calcd for $C_{22}H_{26}N_4O_5S$ (458.53): C, 57.63; H, 5.72; N, 12.22; S, 6.99%, Found: C, 57.59; H, 5.79; N, 12.18; S, 6.91%.

Ethyl 5'-amino-6'-cyano-4'-oxo-1'-phenyl-3',4'-dihydro-1'H-spiro(piperidine-4,2'-thieno[2,3-*d*]pyrimidine)-1-carboxylate (9b). Pale brown, yield 80%, mp 245-248 °C, IR (υ_{max}, cm^{-1}): 3403-3318 (NH_2), 3165 (NH), 2175 (CN), 1697 (C=O, ester), 1659 (C=O). ^1H NMR (300 MHz, DMSO-d_6), δ_H 1.09 (3H, t, J = 7.2 Hz, CH_3), 1.43-1.51(2H, m, CH_2), 2.11-2.15 (2H, m, CH_2), 3.17-3.21 (2H, m, CH_2), 3.81-3.85 (2H, m, CH_2), 3.95 (2H, q, J = 7.2 Hz, OCH_2), 6.80

(2H, s, NH_2, D_2O-exchangeable), 7.42-7.56 ($5H_{aro}$, m, 5CH), 8.37 (1H, s, NH, D_2O-exchangeable). MS, *m/z*, (%) = 411.65 (M^+, 89.36), 82.08 (C_4H_4NO, 100). Anal. Calcd for $C_{20}H_{21}N_5O_3S$ (411.48): C, 58.38; H, 5.14; N, 17.02; S, 7.79%, Found: C, 58.29; H, 5.23; N, 16.96; S, 7.72%.

9-Benzyl-3-cyano-2-methylthio-4-oxo-1-phenyl-1,5,9-triazaspiro[5.5]undec-2-ene (10). To a stirred 0.75 N aqueous KOH solution (20 mL), compound **3b** (10 mmol) and dimethyl sulfate (20 mmol) were added successively. A resulting precipitate was filtered off, washed with water, dried and recrystallized from ethanol. Pale yellow crystal, yield 79%, mp 208-210 °C, IR (υ_{max}, cm^{-1}): 3169 (NH), 3049 (Ar-H), 2927 (Alph-H), 2210 (CN), 1644 (C=O). ^1H NMR (300 MHz, DMSO-d_6), δ_H 1.67-1.70 (2H, m, CH_2), 1.85-1.89 (2H, m, CH_2), 2.26 (2H, m, CH_2), 2.33 (3H, s, SCH_3), 2.57-2.60 (2H, m, CH_2), 3.42 (2H, s, NCH_2), 7.23-7.45 ($10H_{aro}$, m, 10CH), 8.15 (1H, s, NH, D_2O-exchangeable). MS, *m/z*, (%) = 404.50 (M^+, 2.09), 90.85 (C_7H_7, 100). Anal. Calcd for $C_{23}H_{24}N_4OS$ (404.53): C, 68.29; H, 5.98; N, 13.85, S, 7.93%. Found; C, 68.23; H, 6.11; N, 13.78; S, 7.89%.

9-Benzyl-3-cyano-2-ethylthio-4-oxo-1-phenyl-1,5,9-triazaspiro[5.5]undec-2-ene (11). Ethyl iodide (2mmol) was added to a mixture of **3b** (10 mmol) and anhydrous potassium carbonate (20 mmol) in DMF (5mL). The reaction mixture was stirred for 18-20 h at room temperature and then poured into cold water. After stirring for 15 minutes, the precipitated product was collected by filtration, washed with water, dried and recrystallized from ethanol. Yellow crystal, yield 75%, mp 208 °C, IR (υ_{max}, cm^{-1}): 3181 (NH), 3051(Ar-H), 2928 (Alph-H), 2210 (CN), 1644 (C=O). ^1H NMR (300 MHz, DMSO-d_6), δ_H 1.10 (3H, t, J = 7.2 Hz, CH_3), 1.68-1.69 (2H, m, CH_2), 1.88-1.92 (2H, m, CH_2), 2.27 (2H, m, CH_2), 2.58-2.62 (2H, m, CH_2), 2.84 (2H, q, J = 7.5 Hz, SCH_2), 3.44 (2H, s, NCH_2), 7.22-7.48 ($10H_{aro}$, m, 10CH), 8.18 (1H, s, NH, D_2O-exchangeable). MS, *m/z*, (%) = 419.05 (M^+, 1.49%), 90.85 (C_7H_7, 100%). Anal. Calcd for $C_{24}H_{26}N_4OS$ (418.55): C, 68.87; H, 6.26; N, 13.39; S, 7.66%, Found: C, 68.82; H, 6.31; N, 13.31; S, 7.59%.

3-Cyano-5,9-dibenzyl-2-(benzylthio)-4-oxo-1-phenyl-1,5,9-triazaspiro[5.5]-undec-2-ene (12). A mixture of compound **3b** (10 mmol), benzyl chloride (10 mmol), and triethylamine (2.1 mL, 1.5 mmol) in ethanol (20 mL), the reaction was continued for 2h., a white precipitate was formed after cooling. A resulting precipitate was filtered off, dried, and recrystallized from ethanol. White crystal, yield 80%, mp 180-182 °C, IR (υ_{max}, cm^{-1}): 3065 (Ar-H), 2995 (Alph-H), 2220 (CN), 1665 (C=O). ^1H NMR (300 MHz, $CDCl_3$), δ_H 1.67 (2H, m, CH_2), 1.95-1.99 (2H, m, CH_2), 2.22 (2H, m, CH_2), 2.74 (20H, m, CH_2), 3.50 (2H, s, NCH_2Ph), 4.20 (2H, s, SCH_2), 4.68 (2H, s, NCH_2Ph), 6.84-7.44 ($20H_{aro}$, m, 20CH). ^{13}C NMR (75 MHz, $CDCl_3$), δ_C 34.45 ($2CH_2$), 39.09 (SCH_2), 43.79 (NCH_2), 48.34 ($2CH_2$), 62.00 (NCH_2), 69.10 (C-6), 73.04 (C-3), 116.96 (CN), 126.00, 127.90, 128.31, 128.65, 129,14, 129.33, 129.66, 135.35, 138.44 (C-Ar), 172.86 (C=O), 173.01 (C-2), MS, *m/z*, (%) = 572.55 (M^+ + 2, 1.45), 91.05 (C_7H_7, 100). Calcd for $C_{36}H_{34}N_4OS$ (570.75): C, 75.76; H, 6.00; N, 9.82; S, 5.62%, Found: C, 75.69; H, 6.11; N, 9.78; S, 5.59%.

Ethyl 2-(9-benzyl-3-cyano-4-oxo-1-phenyl-1,5,9-triazaspiro[5.5]undec-2-en-2-ylthio)acetate (13). To a stirred 0.75N aqueous KOH solution (20 mL), compound **3b** (10 mmol) and ethyl bromoacetate (20 mmol) were added successively. A resulting precipitate was filtered off, washed with water, dried and recrystallized from ethanol. Grey powder, yield 78%, mp 186-188 °C, IR (υ_{max},cm^{-1}): 3145 (NH), 2931(Alph-H), 2196 (CN), 1698 (C=O, ester), 1642 (C=O). ^{1}H NMR (300 MHz, DMSO-d_6), δ_H 1.18 (3H, t, J = 7.2 Hz, CH_3), 1.64-1.71 (2H, m, CH_2), 1.84-1.88 (2H, m, CH_2), 2.23-2.31 (2H, m, CH_2), 2.58-2.62 (m, 2H, CH_2), 3.45 (2H, s, NCH_2Ph), 3.70 (2H, s, SCH_2), 4.09 (2H, q, J = 7.2 Hz, OCH_2), 7.19-7.50 ($10H_{aro}$, m, 10CH), 8.17 (1H, s, NH, D_2O-exchangeable). MS, *m/z*, (%) = 476.20 (M^+, 52.54), 91.10 (C_7H_7, 100). Calcd for $C_{26}H_{28}N_4O_3S$ (476.59): C, 65.52; H, 5.92; N, 11.76; S, 6.73%. Found; C, 65.43; H, 6.01; N, 11.71; S, 6.68%.

5'-Amino-1-benzyl-6'-cyano-4'-oxo-1'-phenyl-3',4'-dihydro-1'H-spiro-[piperidine-4,2'-thieno [2,3-d]pyrimidine] (14). To a stirred 0.75 N aqueous KOH solution (20 mL), compound **3b** (10 mmol) and bromoacetonitrile (20 mmol) were added successively. A resulting precipitate was filtered off, washed with water, dried and recrystallized from ethanol. Pale orange, yield 78%, mp 218-220 °C, IR (υ_{max}, cm^{-1}): 3423-3321 (NH_2), 3208 (NH), 3060 (Ar-H), 2179 (CN), 1653 (C=O). ^{1}H NMR (300 MHz, DMSO-d_6), δ_H 1.58-1.60 (2H, m, CH_2), 2.05-2.09 (2H, m, CH_2), 2.37-2.42 (2H, m, CH_2), 2.56-2.60 (2H, m, CH_2), 3.42 (2H, s, NCH_2Ph), 6.78 (2H, s, NH_2, D_2O-exchangeable), 7.18-7.57 ($10H_{aro}$, m, 10CH), 8.09 (1H, s, NH, D_2O-exchangeable). MS, *m/z*, (%) = 429.60 (M^+, 65.59), 282.50 ($C_{14}H_{10}N_4OS$, 100), 90.80 (C_7H_7, 100%). Calcd for $C_{24}H_{23}N_5OS$ (429.54): C, 67.11; H, 5.40; N, 16.30; S, 7.47%, Found: C, 66.98; H, 5.49; N, 16.23; S, 7.36%.

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